# Chimiothérapie en réanimation pour la prise en charge des défaillances d'organes liées aux cancers solides

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**THESE D'ETAT DE DOCTEUR EN MEDECINE**
**Mention Spécialité**

**Le Vendredi 23 Septembre 2016 à 14 heures**

Salle des thèses - Bâtiment E – 2ème étage
3, rue des Louvels

# Monsieur Yoann ZERBIB

**TITRE DE LA THESE :**

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Vu : les Membres de Jury

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Les Juges,

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**(Réanimation, médecine d'urgence)**

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**Chef du service d'hématologie clinique et de thérapie cellulaire**

**Chef du Pôle « Oncopôle »**

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**Chef du service d'Oncologie médicale**

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**ABREVIATIONS:**

- **COPD :** Chronic Obstructive Pulmonary Disease
- **GRRROH :** Groupe de Recherche en Réanimation Respiratoire Onco-Hématologique
- **HLH :** Hemophagocytic Lymphohistiocytosis
- **ICU :** Intensive Care Unit
- **NSCLC :** Non Small Cell Lung Cancer
- **SAPS2 :** Simplified Acute Physiology Score 2
- **SCLC :** Small Cell Lung Cancer
- **SOFA :** Sequential Organ Failure Assessment
- **SRLF :** Société de Réanimation de Langue Française
- **TMA :** Thrombotic Microangiopathy

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# Urgent chemotherapy for life-threatening complications related to solid neoplasms

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# Abstract

**Background**: Malignancies can be directly responsible for organ failures at the time of diagnosis or relapse. The management of such specific complications relies on urgent chemotherapy and eventual instrumental or surgical procedures, combined with advanced life support. However relevant data about their outcomes are lacking.

**Methods**: We performed a multicenter retrospective (2000-2015) study which included adult patients who received urgent chemotherapy in the intensive care unit (ICU) for organ failure related to solid neoplasms. The modalities of chemotherapy, requirements of adjuvant instrumental or surgical procedures and organ supports were collected. Endpoints were short- and long-term survival rates.

**Results**: 136 patients were included. Lung cancer was the most common malignancy distributed into small cell lung cancer (SCLC, n=57) and non-small cell lung cancer (NSCLC, n=33). The main reason for ICU admission was acute respiratory failure in 111 (81.6%) patients, of whom 89 required invasive mechanical ventilation. Compression and tissue infiltration by tumor cells were the leading mechanisms resulting in organ involvement in 78 (57.4%) and 47 (34.6%) patients. The overall in-ICU, in-hospital, 6-month and one-year mortality rates were 37%, 58%, 74% and 88%, respectively. SCLC was identified as an independent predictor of hospital survival. However this gain in survival was not sustained since the one-year survival rates of SCLC, NSCLC and non-lung cancer patients all dropped below 20%.

**Conclusions**: Urgent chemotherapy along with aggressive management of organ failures in the ICU can be life-saving in a number of cancer patients, most especially for SCLC, although the long-term survival is hardly sustainable.



**Keywords: Lung neoplasm, Chemotherapy, Intensive Care Unit**

# Résumé

**Contexte:** Les cancers solides peuvent être responsables de défaillances d'organes spécifiques. La gestion de ces complications repose sur l'administration urgente de chimiothérapie, sur d'éventuelles procédures instrumentales ou chirurgicales et sur un support d'organe en réanimation. Cependant, les données sur la prise en charge et le pronostic de ces patients sont rares dans la littérature.

**Méthodes:** Nous avons réalisé une étude rétrospective (2000-2015) multicentrique ayant inclus des patients adultes ayant reçu une chimiothérapie en urgence en réanimation pour le traitement d'une défaillance d'organe attribuée à un cancer solide. Les modalités de la chimiothérapie, le recours à des traitements adjuvants instrumentaux ou chirurgicaux ainsi que les suppléances d'organe ont notamment été collectés. Les critères d'évaluation étaient la survie à court et long terme.

**Résultats:** 136 patients ont été inclus. Les tumeurs broncho-pulmonaires étaient largement prédominantes (n=90, 66%), réparties entre cancer du poumon à petites cellules (CPC, n = 57) et cancer du poumon non à petites cellules (CPNPC, n = 33). Le principal motif d'admission en réanimation était l'insuffisance respiratoire aiguë chez 111 patients (81,6%), dont 89 ont eu recours à une ventilation mécanique invasive. La compression d'organe et l'infiltration tissulaire par des cellules tumorales étaient les mécanismes responsables de la défaillance d'organes chez 78 (57,4%) et 47 (34,6%) patients respectivement. La mortalité en réanimation, à l'hôpital, à 6 mois et à un an était de 37%, 58%, 74% et 88%, respectivement. Le CPC a été identifié comme un facteur pronostique indépendamment associé à une meilleure survie hospitalière. Le bénéfice sur la survie n'était cependant pas maintenu à 1 an. La mortalité globale à un an des patients atteints de cancer broncho-pulmonaire était de 88%, sans différences en fonction du type cellulaire.

**Conclusions:** La prescription de chimiothérapie en urgence associée à une prise en charge invasive des défaillances d'organes en USI peut être bénéfique chez certains patients atteints de cancer, plus particulièrement au cours du CPC. Le pronostic à long terme reste sombre.



**Mots clés : Cancer Broncho-pulmonaire, Chimiothérapie, Réanimation**

# Résumé détaillé


## Introduction

Grâce aux progrès obtenus dans le traitement du cancer et de la prise en charge des défaillances d'organes, le pronostic des patients d'onco-hématologie admis en réanimation s'est amélioré au cours des dernières années. Si l'admission en réanimation des patients d'oncologie est le plus communément liée à la toxicité des thérapeutiques anti-cancéreuses telles que la chimiothérapie ou la chirurgie, elle est plus rarement motivée par une complication spécifique de la maladie. La gestion de ces complications repose alors sur l'administration urgente de chimiothérapie et sur d'éventuelles procédures instrumentales ou chirurgicales, sous couvert d'éventuels supports de défaillances d'organes. Les données jusqu'alors disponibles concernent essentiellement les patients atteints d'hémopathies malignes et sont difficilement extrapolables aux patients atteints de cancer solide. L'objectif de notre étude était donc de décrire les situations et les défaillances d'organes liées à un cancer solide qui imposent la prescription urgente de chimiothérapie en réanimation et d'identifier les facteurs pronostiques.

## Patients et méthodes

Nous avons réalisé une étude observationnelle rétrospective entre 2000 et 2016, incluant 16 centres du Groupe de Recherche en Réanimation Respiratoire Onco-Hématologique (GrrrOH). Les patients adultes atteints de néoplasie solide responsable d'une défaillance d'organe et recevant une chimiothérapie en réanimation étaient éligibles.

Les données démographiques, l'état fonctionnel (performans status), les antécédents, les caractéristiques du cancer, les modalités d'administration de la chimiothérapie, le motif d'admission et le mécanisme de la défaillance d'organe ont été collectés. La sévérité à l'admission était évaluée par le Simplified Acute Physiology Score (SAPS) II et le score Sequential Organ Failure Assessment (SOFA). Le recours aux supports de défaillances d'organes a également été collecté (ventilation mécanique, épuration extrarénale, vasopresseur). La survie a été évaluée à la sortie de réanimation, à la sortie de l'hôpital, à 6 mois et à 1 an.

**Résultats**

Cent cinquante et un patients ont reçu une chimiothérapie en réanimation pendant la période d'inclusion de 16 ans, dont 136 ont été inclus dans l'analyse (15 patients ont été exclus car ne présentaient pas de défaillance d'organe en lien avec le cancer). Le cancer pulmonaire était le plus fréquemment rencontré (n=90), répartit entre cancer pulmonaire à petites cellules (CPC) (n=57) et non à petites cellules (CPNPC) (n=33). La maladie était souvent métastatique d'emblée (n=82, 60,3%). Il s'agissait le plus souvent d'une complication inaugurale (n=122, 89,7%), et le cancer étant de fait diagnostiqué en réanimation chez 80 patients (58,9%). Le motif principal d'hospitalisation était la détresse respiratoire aiguë (n=111, 81,6%). Une compression d'organe (n=78) et une infiltration tissulaire (n=47) étaient les principaux mécanismes responsables de la défaillance d'organe.

Le traitement a consisté en une poly-chimiothérapie chez 120 patients et une mono-chimiothérapie chez 16 patients. Une réduction de dose a été nécessaire pour 20% des patients, évaluables le plus souvent liée à la présence d'une insuffisance rénale sous-jacente. La séquence de chimiothérapie a été modifiée pour 18% des patients évaluables. 34 patients (25%) ont bénéficié de procédures adjuvantes instrumentales ou chirurgicales.

En ce qui concerne les supports de défaillances d'organes, 89 patients ont eu recours à une ventilation mécanique invasive pour une durée médiane de 13 jours (5-25). 47 patients ont reçu une ventilation mécanique non-invasive, mais 32 d'entre eux ont finalement requis une intubation oro-trachéale.

La mortalité en réanimation était de 37% (n=50). 29 patients supplémentaires sont décédés à l'hôpital, aboutissant à une mortalité hospitalière de 68%. La mortalité à 6 mois et 1 an était de 74% et 88% respectivement.

Les facteurs associés à la mortalité hospitalière ont été étudiés. Le pronostic des patients atteints de cancer pulmonaire était différent selon le type histologique des taux de mortalité hospitalière de 49 et 70% pour les CPC et les CPNPC respectivement. La nature et la sévérité de la défaillance d'organe demeuraient néanmoins les principaux déterminants de la mortalité hospitalière. Après ajustement sur le mécanisme de la défaillance d'organe, le caractère métastatique, la prescription d'une poly-chimiothérapie, l'âge et le score SOFA à l'admission, la présence d'un CPC restait indépendamment associé à la survie hospitalière (Odds ratio,0,44 [0,20-0,94], p=0,03).

**Discussion**

Nous rapportons ici la plus large cohorte de patients ayant présenté une défaillance d'organe spécifique en lien avec un cancer solide, ayant motivé une chimiothérapie instituée en urgence en réanimation. Une revue de la littérature nous a permis d'identifier 54 patients remplissant les critères d'inclusion de notre étude et présentant un taux de survie à court terme comparable à 39%. De manière intéressante, nous avons identifié le CPC comme facteur indépendamment associé à la survie hospitalière, quelque soit l'extension de la maladie.

L'administration de chimiothérapie est la principale action thérapeutique permettant une résolution rapide de la défaillance d'organe. Cependant, plusieurs facteurs comme la variation du volume de distribution ou la diminution des taux sériques protéiques exposent à un risque de sous-dosage ou surdosage et de toxicité. La présence d'une insuffisance rénale et/ou d'une épuration extra-rénale impose l'adaptation de dose ou de séquence d'administration du traitement. En revanche, il n'y a pas de recommandations claires sur la nécessité d'adapter la posologie au poids ou à la surface corporelle réelle. Toutes ces contraintes représentent un enjeu majeur pour l'oncologue et le réanimateur, l'optimisation des doses de chimiothérapie chez ces patients critiques représente un axe de recherche potentiel mais encore vierge.

Si les résultats sur la survie hospitalière sont encourageants, ils sont à pondérer avec le pronostic très péjoratif à 1 an. Plusieurs facteurs non prédictibles ont un impact sur le pronostic, comme la réponse à la première ligne de traitement, la possibilité de poursuivre la chimiothérapie. Ces résultats imposent de définir un projet thérapeutique réaliste prenant en compte le pronostic à long terme. Dans ce cas, il peut être proposé une réanimation dite « d'attente » en vue de réévaluer le projet thérapeutique après quelques jours d'hospitalisation. Dans notre cohorte, la présence d'une infection acquise en USI et l'apparition de nouvelles complications aboutissent à une décision de limitation des thérapeutiques.

Notre étude présente plusieurs limites. Tout d'abord, le recrutement et l'analyse ont été rétrospectifs et sur une période de 16 ans pendant laquelle des progrès significatifs ont été réalisés que ce soit en réanimation ou en oncologie. Nous n'avons néanmoins pas mis en évidence d'effet temporel sur la survie hospitalière. Ensuite, le recrutement est largement dominé par les cancers pulmonaires, et il est impossible de proposer une analyse plus fine du sous-groupe hétérogène des patients avec cancers non-pulmonaires. D'autre part, les centres participants du réseau de recherche du GRRR-OH sont particulièrement rompus à la prise en

charge diagnostique et thérapeutique des patients d'onco-hématologie sous couvert d'un environnement médico-technique performant. En soi, l'extrapolation de ces résultats à des centres non-experts ne se pose pas, car il nous semble absolument nécessaire que ces patients à très haut risque soient transférés rapidement vers un centre tertiaire spécialisé. Enfin, nous avons choisi comme critère de jugement la mortalité hospitalière ce qui est probablement simpliste dans ce contexte. D'autres critères pertinents comme la qualité de vie chez les patients survivants à la réanimation n'ont pas pu être évalués ici.

**Conclusion**

Dans le cadre d'une prise en charge agressive en réanimation, l'administration de chimiothérapie peut être bénéfique chez certains patients avec défaillance d'organe spécifique, plus particulièrement chez les patients atteints de CPC. Ce travail apporte des données pronostiques pertinentes sur cette situation clinique rare mais non exceptionnelle, et pourra certainement aider à la prise de décision dans cette situation. Néanmoins, dans ce contexte d'un pronostic globalement effroyable à long terme, il nous semble important de rappeler que la prise en charge ne doit cependant pas être guidée uniquement par la survie en réanimation mais doit s'intégrer dans une prise en charge plus globale, prenant en compte le pronostic à long terme, la possibilité ultérieure de poursuivre le traitement anti-cancéreux ainsi que la qualité de vie. Ce processus décisionnel complexe impose une collaboration étroite entre oncologues et réanimateurs.

Article

# Urgent chemotherapy for life-threatening complications related to solid neoplasms

## Introduction

The paradigm concerning ICU referral of patients with malignancies has dramatically changed over the last two decades, following advances in the overall prognosis of cancer(1,2) and improved outcomes of life-threatening complications requiring ICU admission(3–13). A number of studies have allowed refining the triage criteria for ICU admission(14–17). With the exception of patients with poor functional status and/or with end-stage malignant disease, an increasing number of patients with cancer have become liable for ICU admission. This is particularly true for patients with newly diagnosed diseases presenting with specific inaugural complications, since the common prognostic factors related to the underlying malignancy including the response to first-line treatment may not be available yet.

Complications imposed by anticancer treatments such as surgery and cytostatic drugs and radiotherapy account for the large majority of life-threatening conditions that warrant ICU admission. However some patients may exhibit some complications directly related to the underlying malignancy itself at the time of diagnosis or relapse (4,11). Cancer-related organ failures may be related to compression of anatomic structures, tissue infiltration, spontaneous tumor lysis syndrome or other paraneoplastic manifestations. The management of such specific complications relies on urgent chemotherapy(18) and eventual instrumental or surgical procedures, combined with advanced life support. As of today, only four studies have specifically addressed the outcome of critically ill patients with malignancies who received chemotherapy in the ICU for cancer-specific complications(19–22). Their main conclusions were that chemotherapy was feasible and could be lifesaving despite advanced life support. However, these studies involved a large majority of patients with hematological malignancies and whether such results fully extend to patients with solid tumors is questionable. To this aim, we performed a retrospective chart review of patients with organ failures related to solid tumors, and who then required urgent chemotherapy in the ICU along with life support.

## Patients and methods

### *Setting and patients*

We performed a multicenter retrospective (2000-2015) study including 16 centers within the Groupe de Recherche en Réanimation Respiratoire Onco-Hématologique (GrrrOH) research network. Adult patients (> 18 years) who received urgent chemotherapy in the ICU for solid tumor-related organ failure were eligible for the study. Patients were identified by the chemotherapy preparation unit in each hospital. The study was approved by the ethics committee of the Société de Réanimation de Langue Française (SRLF #15-31). Informed consent was waived due to its retrospective and observational design.

### *Data collection*

Demographic data included age and gender. The functional status prior to admission to ICU was evaluated by the Knaus score (A: no limitation of activity; B: mild limitation; C: important limitation; D: major restriction). Non-malignant comorbidities were collected and a modified Charlson score without the malignant comorbidity was computed. The following characteristics related to the presentation and management of cancer were collected: type of tumour and primary organ involvement, first presentation or relapse, metastatic spread, as well as the mechanism of organ failures (organ compression, organ infiltration or paraneoplastic manifestations).

Severity and organ failure scores were calculated on the first day of ICU admission through a modified Simplified Acute Physiology Score (SAPS) II (without the immunodepression item) and the Sequential Organ Failure Assessment (SOFA) score. The modalities of administration of chemotherapy were collected (type of drugs, sequential regimen, dosing reduction) as well as adjuvant palliative measures to rapidly restore appropriate organ functions such as instrumental procedures (draining, insertion of prothesis, arterio-embolisation) radiotherapy or surgery. Requirements of organ supports were recorded throughout the stay in the ICU, and included invasive and non-invasive ventilation vasopressors and renal replacement therapy. The outcome endpoints were in-ICU, in-hospital, 6-month and one-year mortality rates. Decisions of withholding and withdrawing life supports were taken on collectively.

### *Statistical analysis*

Continuous variables were expressed as median and interquartile range ($25^{th}$ and $75^{th}$ percentiles) and were compared by using the Mann-Whitney test. Categorical variables were expressed as numbers and percentages and were compared by the Chi-square test or the Fisher

exact test as appropriate. Variables found associated with a p value < 0.20 in univariate analysis were entered into a multivariate backward stepwise logistic regression analysis in order to identify the factors independently associated with in-hospital mortality. The goodness-of-fit of the model was checked by the Hosmer-Lemeshow test. The cumulated survival curves were built using the Kaplan-Meier method and compared by the log-rank test.

## Results

### *Study cohort*

During the 16-year inclusion period, 151 patients with solid cancer received chemotherapy in the 16 participating ICUs (figure 1). Fifteen patients were excluded from the analysis because administration of chemotherapy in the ICU was not indicated by organ failures but rather required by specific supervision (allergic reaction (n=11), minor hemoptysis (n=2), post-operative monitoring after pleurodesis (n=1) and pneumothorax complicating venous access port insertion (n=1)), leaving 136 patients who were finally included in the study (table 1). Three patients were lost to follow-up at 6 months and four additional ones were lost to follow-up at one year. The follow-up did not reach one year in three recent patients. Although patients were relatively young (age 60 (50-67) years), most of them (70%) displayed severe functional alteration as assessed by a Knaus score of C or D.

The most common underlying malignancy was lung cancer (n=90), distributed between small cell lung cancer (SCLC) (n=57) and non-small cell lung cancer (NSCLC) (n=33). One patient had concurrent lung (NSCLC) and digestive tumours and was by default considered to have lung cancer. Most malignancies were newly diagnosed (n=122, 89.7%), the diagnosis being made in the ICU for 80 patients (58.9%). The majority of patients (n=82, 60.3%) had metastasis.

### *Cancer-related organ failures*

Most patients (n=95) were admitted to the ICU directly from home or from the emergency department. The main reason for ICU admission was acute respiratory failure including one episode complicated by hypoxic cardiac arrest (table 2). Compression (n=78) and infiltration (n=47) were the leading mechanisms of organ involvement by malignant tumours. Upper vena cava syndrome was observed in 18 patients (13.2%) and pulmonary embolism in 13 patients (9.6%). Other indications for ICU admission relied on paraneoplastic manifestations in 11 cases, including hematologic disorders (thrombotic microangiopathy (3) and hemophagocytic lymphohistiocytosis (1)), peripheral neurologic disorders resulting in acute respiratory failure (severe peripheral neuropathy (3), dermatopolymyositis (1), myasthenia (1)) and coma (opsonus myoclonus syndrome (1), encephalitis (1))

***Specific management of cancer***

The treatment was based on combined and single chemotherapy in 120 (88.2%) and 16 (11.8%) patients, respectively (table 2). Most chemotherapy combination regimens were based on platin salts. The modalities of chemotherapy administration in this setting were addressed in 101 patients, with respect to the common regimen usually indicated for the underlying malignancy. The dosing was reduced in 20 patients (20%) mostly linked to renal failure, and the sequence of drug administration was modified in 18 patients (18%).

Thirty-four patients (25%) required either instrumental or surgical adjuvant procedures. Among them, 22 required pleural draining, nine required decompressive prosthesis insertion (tracheo-bronchial (n=7), upper vena cava (n=1), intestinal (n=1)), three underwent arterio-embolisation for major hemoptysis, and 12 required surgery (pericardial draining (n=4), pleurodesis (n=3), urinary draining (n=1), decompressive laminectomy (n=1), percutaneous cementoplasty (n=1), diagnostic uterine appendage resection (n=1) and lung lobar resection (n=1)). Initiation of chemotherapy resulted in tumor lysis syndrome in 10 patients, of whom four developed acute renal failure requiring renal replacement therapy. Fourty patients displayed chemotherapy-induced neutropenia and two patients displayed severe enterocolitis as a consequence of major mucosal damage.

***General management in the ICU***

With respect to the very high prevalence of acute respiratory failure, a ventilatory support was applied in most patients (table 2). Thus, 47 patients received ventilatory support through non-invasive ventilation of whom 32 subsequently required endotracheal intubation. Overall, 89 patients received invasive mechanical ventilation with duration of 13 (5 - 25) days. 39 patients required vasopressors (28,7%) and 11 required renal replacement therapy (8,1%). Acute renal failure was attributed to septic shock (n=8) and/or tumor lysis syndrome (n=4). Veno-venous ECMO was deemed necessary in one patient with refractory respiratory failure. The in-ICU length of stay was 13 (7-26) days. Following chemotherapy, 68 (50%) and 14 (10%) patients developed ICU-acquired infections and severe hemorrhage, respectively.

***Determinants of outcome***

The in-ICU mortality rate was 37% (50/136 patients), and followed end-of-life decisions in 46 patients. The in-ICU length of stay in survivors was 10 (7-23) days. In addition, a significant number of ICU survivors subsequently died in the hospital, resulting in an in-

hospital mortality rate of 58%. The 6-month and one-year mortality rates were 74% and 88%, respectively (figure 1). We did not observe any changes in survival over the study period (data not shown). All but four hospital survivors were able to further receive maintenance chemotherapy. The main characteristics of the 15 one-year survivors are shown in the table 3.

We addressed the determinants of hospital outcome by comparing the characteristics of survivors and deceased patients. Although not significant, some features of the underlying malignancy tended to be associated with outcome. The outcome of patients with lung cancer was not consistent across histological subtypes, since the mortality rates of patients with SCLC and NSCLC were 49% and 70%, respectively. The metastatic status also tended to be associated with a worse outcome. Patients with combined chemotherapy regimens fared better that those with single drug regimens. Finally, the nature and extent of organ failures, either by severity scores or requirements of invasive mechanical ventilation and vasopressors were the most potent determinants of outcome. In a multivariate logistic regression analysis adjusted with age, admission SOFA score, the mechanism of organ failure, the metastatic status and the use of combination chemotherapy, with hospital mortality as the dependent variable, the presence of SCLC remained independently associated with improved hospital survival (odds ratio 0.44 [0.20-0.94], p= 0.03). A consistent trend was observed when adjusted with the modified SAPS2 score instead of age and SOFA score (odds ratio 0.42 [0.19-0.92], p= 0.03).

**Discussion**

It is now generally accepted that full-code intensive care management should be offered to cancer patients in first-line of treatment, and obviously in those in remission. This applies to patients with inaugural complications of malignancies, although this assumption is largely derived from the encouraging results obtained in patients with complicated hematological malignancies(20,23–25). Thanks to our multicenter research network, we herein report the largest original cohort of patients presenting with organ failures that could be directly related to solid tumours. A subset of cancer patients may undoubtedly benefit from urgent chemotherapy along with advanced life support. Importantly, the type of malignancy may help stratifying the risk of early deaths and therefore the level of care in this setting. Patients with SCLC, a tumour reckoned to be highly proliferative and usually very susceptible to chemotherapy, were more likely to be discharged from hospital. However, we acknowledge that the short-term survival gain was generally not sustained since the majority of hospital survivors died within one year although most of them had been able to receive maintenance chemotherapy thereafter.

As mentioned above, investigations in the field have mainly involved patients with hematological malignancies including acute leukemia and high-grade lymphoma which are more likely to result in organ dysfunctions. This is explained by both the high proliferative activity and aberrant functions of malignant cells. Those characteristics also underlie the fast response to chemotherapy, although it may also precipitate or worsen organ dysfunctions through unleashed tumor lysis syndrome(26,27). Four recent studies have addressed the outcome of patients with malignancies who received chemotherapy in the ICU(19–22). Three of them also included a few patients with solid tumors(19,21,22). In addition, a few series of patients with lung cancer admitted to the ICU admission mentioned the requirement for urgent chemotherapy in the ICU. Altogether, these cohorts gathered 54 patients who fulfilled the inclusion criteria of the present study and who exhibited a similar short-term survival rate of 39%(11–13,19,22)

We identified SCLC as independently associated with a good outcome although a number of patients presented with concurrent metastatic spread. Although the benefit dos not seem to be fully sustained over the next year following discharge, patients with SCLC are certainly liable to maximal life support. This is probably linked to the particular susceptibility of SCLC to chemotherapy as illustrated by the occurrence of tumor lysis syndrome uncommonly

encountered on solid tumors. In contrast NSCLC are usually poorly susceptible to cytostatic chemotherapy. Importantly, some adenocarcimal tumours may exhibit particular molecular patterns making them liable to targeted therapies. Case series are increasingly reporting the potential of such targeted therapies to reverse acute respiratory failure related to lung cancer harboring particular oncogenic mutations(28,29). Only seven patients with lung and renal adenocarcinoma received targeted therapy in the present study, of whom four survived the hospital stay. Current advances in the comprehension of molecular events leading to cancer will certainly result in striking changes in the prognostic assessment and in major therapeutic implications(1,2), and therefore should prevent us to establish definitive recommendations in this rapidly evolving field.

Administration of cytostatic chemotherapy is the main therapeutic action for fast recovery of organ failures. Cytostatic agents have tight therapeutic index with a major potential of toxicity onto non-malignant dividing cells. Dosing of chemotherapy remains a major challenge in critically ill patients owing to a number of factors that may result in underdosing or conversely overdosing. In general, it remains unclear whether chemotherapy should be adapted to actual or ideal body surface area. Low serum protein levels may increase the toxicity of protein-bound compounds, as already suggested for methotrexate, and may indicate substitution with albumin prior to drug infusion. Distribution volumes are commonly increased in critically ill patients, due to systemic inflammatory response, edema related to abundant fluid administration and/or to renal failure, and sometimes to extra-corporeal circulations for renal replacement therapy or membrane oxygenation. Both renal failure and application of renal replacement therapy may impose adapted dosing and/or administration timing for the most common drugs used in this indication (platin salts, etoposide, cyclophosphamide, methotrexate)(30).

We understand that our results can be perceived differently among readers, since the encouraging hospital survival rate is actually challenged by the considerable mortality within one year. The long-term prognosis is likely to be impacted by multiple predictable and non-predictable factors, including the crude prognosis if the malignancy, response to first-line treatment, the possibility of maintenance chemotherapy, as well as the development of additional complications. Beyond the early step of urgent management with the primary aim of ICU discharge, a comprehensive assessment of the long-term prognosis including both the characteristics of tumors and patients is needed in order to define a realistic therapeutic

project. This probably cannot be accurately achieved at the time of admission but rather after a few days in the ICU, the so-called ICU trial in which patients are first subjected to full-code management before reappraisal of the expected benefits of sustained intensive care (31). Accordingly, the development of ICU-acquired infections prompted end-of-life decisions in a number of our patients. Along this line, the ICU survivors who died in the hospital had not been readmitted to the ICU, also suggesting the implementation of therapeutic limitations.

Some limitations have to be acknowledged. Collection of patients and data was retrospective, but we believe that requests by the chemotherapy preparation units allowed us an accurate and exhaustive identification of patients who received chemotherapy in the ICU. Patients were included over a 16-year period during which significant advances have been achieved both in the treatment of cancer and in the management in the ICU, but we did not identify any temporal trend in outcome. Whereas the numbers of patients with SCLC and NSCLC made them liable to a relatively comprehensive analysis, non-lung cancer patients had various malignancies, making it impossible to draw any definitive conclusions. Most importantly, the study involved 16 centers from the GRRROH research network, which are highly experienced in the management of patients with cancer owing to oncology units with privileged medical and technical environment. Whether our results may apply to less experienced centers remains elusive. However it is worth mentioning that the management of such patients requires various competencies, thereby strongly arguing for referral to tertiary centers with both ICU and oncology teams experienced in the management of critically ill cancer patients(12). Finally, a major limit certainly lies in the endpoints we chose. Survival is of course a major endpoint, but probably too simplistic in the course of cancer. Besides, important additional criteria such as quality of life and the possibility for maintenance of anticancer treatment after ICU discharge are relevant to cancer patients but could not be reliably collected in the present study. A prospective trial by our group is currently evaluating these endpoints in cancer patients who survived the ICU (ClinicalTrials.gov identifier NCT02398890).

## Conclusion

A number of cancer patients with specific organ failures may benefit from urgent chemotherapy along with aggressive management in the ICU, most especially in those with SCLC. However, our management of such patients should not only be guided by the primary goal of ICU discharge, but should take into account the possibility of maintenance anticancer treatment and the probability of remission and prolonged survival thereafter. Such a comprehensive appraisal of the course of the disease imposes a multidisciplinary approach based on close and forthright collaborations between oncologists and intensivists.

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## Tables and figures

### *Table 1: Baseline characteristics of patients*

| Variables | All Patients n=136 | Survivors n= 57 | Deceased n=79 | P |
|---|---|---|---|---|
| **Age, years** | 60 (50.4-67.3) | 61 (50.2-67.4) | 59 (51-67) | 0.74 |
| **Male gender** | 75 (55.1%) | 32 (56%) | 43 (54,4%) | 0.86 |
| **Body mass index, kg/m$^2$** | 23 (19-27) | 22 (19-27) | 23 (20-27) | 0.31 |
| **Knaus score C-D** | 95 (69.9%) | 37 (65%) | 58 (73.4%) | 0.34 |
| **Modified Charlson score** | 2 (1-3) | 2 (0-4) | 2 (1-3) | 0.63 |
| **Non-malignant comorbidities** | | | | |
| COPD | 29 (21%) | 14 (24.6%) | 15 (19%) | 0.52 |
| Chronic cardiac failure | 18 (13.2%) | 6 (11%) | 12 (15.2%) | 0.60 |
| Diabetes | 18 (13.2%) | 9 (16%) | 9 (11.4%) | 0.45 |
| Cirrhosis | 5 (3.7%) | 2 (4%) | 3 (3.8%) | 1 |
| Chronic renal failure | 3 (2.2%) | 1 (2%) | 2 (2.5%) | 1 |
| **Type of cancer** | | | | 0.14 |
| SCLC | 57 (42%) | 29 (50.9%) | 28 (35.4%) | |
| NSCLC | 33 (24%) | 10 (17.5%) | 23 (29.1%) | |
| Non-lung cancer | 46 (34%) | 18 (31.6%) | 28 (35.4%) | |
| **Cancer Status** | | | | 0.77 |
| Newly diagnosed | 122 (89.7%) | 52 (91.2%) | 70 (88,6%) | |
| Relapse/Progression | 14 (10.3%) | 5 (8.8%) | 9 (11,4%) | |
| **Metastatic** | 82 (60.3%) | 29 (51%) | 53 (67.1%) | 0.07 |

*Table 2: Severity and management in the intensive care unit*

| Variables | All Patients n=136 | Survivors n= 57 | Deceased n=79 | *P* |
|---|---|---|---|---|
| **Admission severity scores** | | | | |
| Modified SAPS2, points | 34 (24-46.3) | 29 (22-38) | 38 (26-50.5) | 0.001 |
| SOFA, points | 4 (3-6) | 3 (2-5) | 5 (4-7) | <0.0001 |
| **Primary cause for ICU admission** | | | | 0.58 |
| Acute respiratory failure | 111 (81.6%) | 46 (87.1%) | 65 (82.3%) | |
| Neurological failure | 9 (6.6%) | 5 (8.8%) | 4 (5.1%) | |
| Shock | 7 (5.1%) | 4 (7%) | 3 (3.8%) | |
| Miscellaneous [1] | 9 (6.6%) | 2 (3.5%) | 7 (9%) | |
| **Concomitant infection** | 35 (25.7%) | 16 (28%) | 19 (24%) | 0.69 |
| **Mechanisms of organ failure** | | | | 0.10 |
| Compression | 78 (57.4%) | 37 (59.6%) | 41 (51.9%) | |
| Infiltration | 47 (34.6%) | 14 (24.6%) | 33 (41.8%) | |
| Others [2] | 11 (8.1%) | 6 (10.5%) | 5 (6.3%) | |
| **Chemotherapy** | | | | |
| Combination chemotherapy | 120 (88.2%) | 54 (94.7%) | 66 (83.3%) | 0.06 |
| Dose reduction [3] | 20 (19.8%) | 10 (24.4%) | 10 (16.6%) | 0.44 |
| Modified sequence [3] | 18 (17.8%) | 8 (19.5%) | 10 (16.6%) | 0.8 |
| **Adjuvant treatments** | | | | |
| Instrumental | 34 (25%) | 13 (22.8%) | 21 (26.6%) | 0.69 |
| Draining | 22 (16.2%) | 9 (15.8%) | 13 (16.5%) | 0.73 |
| Prosthesis insertion | 9 (6.6%) | 3 (5.2%) | 6 (7.6%) | 1 |
| Arterial embolisation | 3 (2.2%) | 1 (1.8%) | 2 (2.5%) | 1 |
| Surgery | 12 (8.8%) | 8 (14%) | 4 (5.1%) | 0.12 |
| **Organ failure supports** | | | | |
| Mechanical ventilation | 104 (76.5%) | 38 (66.7%) | 66 (83.5%) | 0.02 |
| Invasive mechanical ventilation | 89 (65.4%) | 31 (54.4%) | 58 (73.4%) | 0.02 |
| Non-invasive mechanical ventilation | 47 (34.6%) | 21 (36.8%) | 26 (32.9%) | 0.71 |
| Vasopressors | 39 (28.7%) | 10 (17.5%) | 29 (36.7%) | 0.02 |
| Renal replacement therapy | 11 (8.1%) | 2 (4%) | 9 (11.4%) | 0.11 |
| Veno-venous ECMO | 1 (0.7%) | 0 | 1 (1.3%) | 1 |

[1] Thrombotic microangiopathy (3), acute renal failure (n=2), hypercalcemia (2), acute liver failure (n=1), hemophagocytic lymphohistiocytosis (1)
[2] Paraneoplastic neuromuscular disorders resulting in acute respiratory failure (severe peripheral neuropathy (3), dermatopolymyositis (1), myasthenia (1)), coma (opsonus myoclonus syndrome (1), encephalitis (1)), thrombotic microangiopathy (3) and hemophagocytic lymphohistiocytosis (1)
[3] Could be reliably addressed on the basis of current treatment guidelines in 101 patients

*Table 3: Characteristics of the 15 one-year survivors*

| Case number | Age | Gender | Type of cancer | First presentation | Metastatic | Reason for ICU admission | Chemotherapy | Instrumental procedures | Admission SOFA score | Life-supporting therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54 | F | Corticosurrenaloma | Yes | Yes | Acute respiratory failure | Carboplatine, Etoposide | 0 | 4 | 0 |
| 2 | 57 | M | Small cell lung cancer | No | Yes | Acute respiratory failure | Carboplatine, Etoposide | 0 | 8 | IMV |
| 3 | 32 | M | Gastric adenocarcinoma | No | Yes | Thrombotic microangiopathy | 5-FU, Oxaliplatine | 0 | 3 | 0 |
| 4 | 65 | F | Small cell lung cancer | No | No | Acute respiratory failure | Carboplatine, Etoposide | 0 | 3 | IMV |
| 5 | 53 | M | Small cell lung cancer | No | No | Opsonus myoclonus syndrome | Cisplatine, Etoposide | 0 | 3 | IMV |
| 6 | 50 | F | Lung adenocarcinoma | No | No | Acute respiratory failure | Endoxan, Cisplatine, Etoposide | 0 | 3 | 0 |
| 7 | 36 | F | Thymic neuroendocrine carcinoma | No | No | Acute respiratory failure | Taxol, Carboplatine | 0 | 1 | 0 |
| 8 | 55 | M | Small cell lung cancer | No | Yes | Acute respiratory failure | Cisplatine, Etoposide, Ifosfamide | Arterial embolisation | 3 | IMV |
| 9 | 31 | M | Lung adenocarcinoma | No | No | Acute respiratory failure | Carboplatine, Taxol, Avastin | 0 | 3 | NIV |
| 10 | 34 | F | Breast carcinoma | No | Yes | Severe sepsis | Doxorubicine, Endoxan | 0 | 1 | 0 |
| 11 | 20 | M | Mediastinal choriocarcinoma | No | Yes | Acute respiratory failure | Cisplatine, Etoposide | Pleural draining | 1 | 0 |
| 12 | 33 | F | Sarcoma | No | Yes | Acute respiratory failure | Doxorubicine, Holoxan, Mesna | Pleural draining | 1 | IMV |
| 13 | 22 | M | Germinal non-seminomatous | No | No | Acute respiratory failure | Cisplatine, Etoposide, Bleomycine | Pleural draining | 1 | 0 |
| 14 | 68 | F | Small cell lung cancer | No | No | Acute respiratory failure | Carboplatine, Etoposide | 0 | 1 | NIV |
| 15 | 65 | F | Breast carcinoma | Yes | Yes | Acute respiratory failure | Taxol | Pleural draining | 2 | 0 |

Abbreviations: ICU, intensive care unit; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation

*Figure 1: Flowchart of the study*

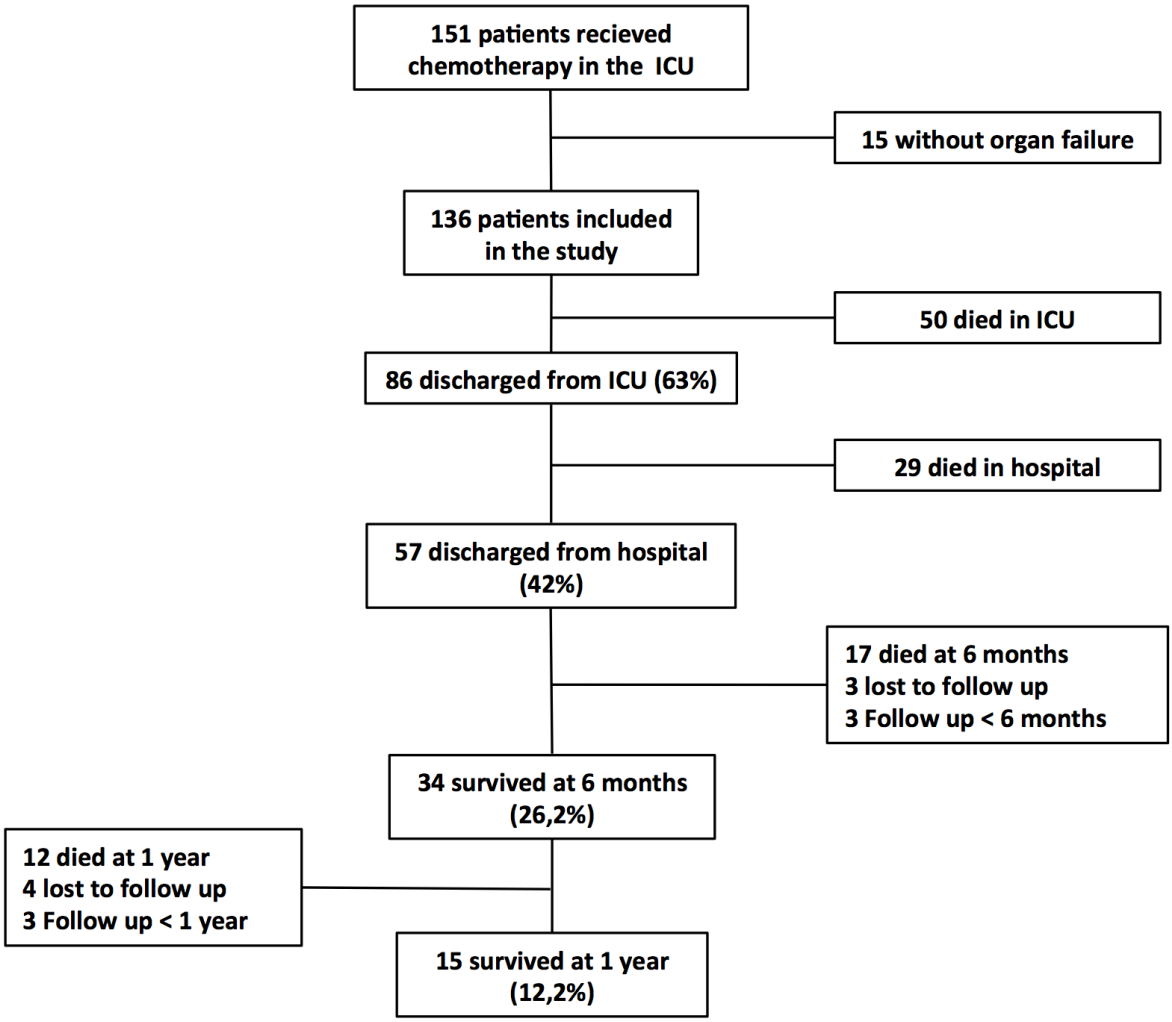
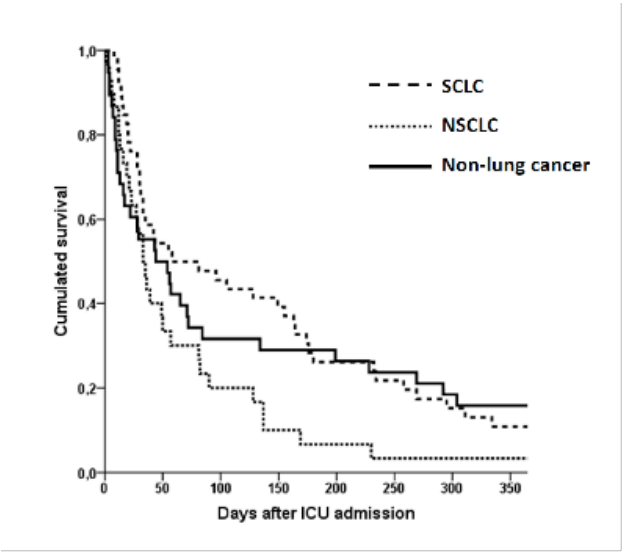
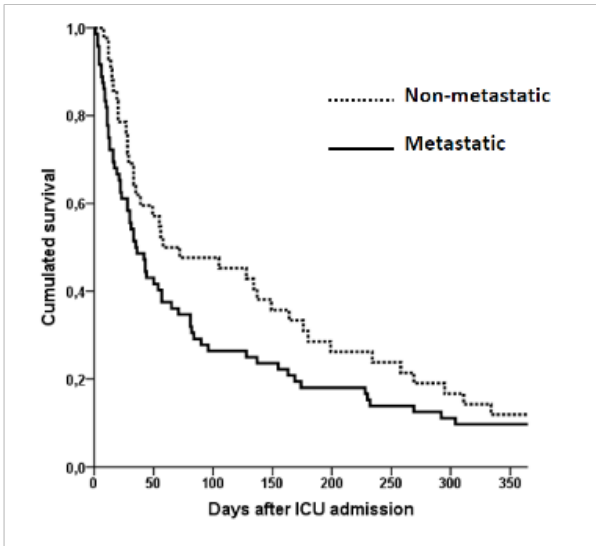


***Figure 2: One-year survival in relevant subgroups of patients***

The cumulated survival was estimated depending on type of cancer (A) and metastatic status (B)

Log-rank test: p=0.07 (A) and 0.10 (B)



# Urgent chemotherapy for life-threatening complications related to solid neoplasms

**Background**: Malignancies can be directly responsible for organ failures at the time of diagnosis or relapse. The management of such specific complications relies on urgent chemotherapy and eventual instrumental or surgical procedures, combined with advanced life support. However relevant data about their outcomes are lacking.

**Methods**: We performed a multicenter retrospective (2000-2015) study which included adult patients who received urgent chemotherapy in the intensive care unit (ICU) for organ failure related to solid neoplasms. The modalities of chemotherapy, requirements of adjuvant instrumental or surgical procedures and organ supports were collected. Endpoints were short- and long-term survival rates.

**Results**: 136 patients were included. Lung cancer was the most common malignancy distributed into small cell lung cancer (SCLC, n=57) and non-small cell lung cancer (NSCLC, n=33). The main reason for ICU admission was acute respiratory failure in 111 (81.6%) patients, of whom 89 required invasive mechanical ventilation. Compression and tissue infiltration by tumor cells were the leading mechanisms resulting in organ involvement in 78 (57.4%) and 47 (34.6%) patients. The overall in-ICU, in-hospital, 6-month and one-year mortality rates were 37%, 58%, 74% and 88%, respectively. SCLC was identified as an independent predictor of hospital survival. However this gain in survival was not sustained since the one-year survival rates of SCLC, NSCLC and non-lung cancer patients all dropped below 20%.

**Conclusions**: Urgent chemotherapy along with aggressive management of organ failures in the ICU can be life-saving in a number of cancer patients, most especially for SCLC, although the long-term survival is hardly sustainable.

**Keywords: Lung neoplasm, Chemotherapy, Intensive Care Unit**